UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/810,796 | 03/15/2001 | Timothy J. Jegla | 018512-005010US | 6783 |

20350 7590 03/12/2003

TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

| EXAMINER | |
|---|---|
| BUNNER, BRIDGET E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 15 |

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/810,796 | JEGLA, TIMOTHY J. | |
| | Examiner | Art Unit | |
| | Bridget E. Bunner | 1647 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *41-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Status of Application, Amendments and/or Claims*

The amendments of 12 October 2001 (Paper No. 6) and 06 June 2002 (Paper No. 10) have been entered in full. Claims 1-40 are cancelled and claims 41-48 are added.

### *Election/Restrictions*

Applicant's election with traverse of Group I, originally filed claims 1-11 and 22-23 in Paper No. 10 (06 June 2002) is acknowledged. The traversal is on the ground(s) that Groups I-IX all stem from a common concept and theory and thus are related. Applicant also contends that prosecution of the claims of Groups I-IX would not place a substantially greater burden on the Examiner. This is not found persuasive because the claims corresponding to claims II-IX have been cancelled, therefore rendering this argument moot. However, if the claims corresponding to Groups II-IX were pending, Applicant's argument still would not be found persuasive. As set forth at pages 2-5 of the previous Office Action of 30 April 2002 (Paper No. 9), the Examiner discussed in detail why the claims of Groups I-IX (or A-I) are considered separate inventions. Basically, the product inventions of Groups A, C-D are distict physically and functionally and are not required one for the other. The different inventions of Groups B and E-I require different ingredients, process steps, and endpoints. Furthermore, each of the inventions of A-I (I-IX) is directed to recognized divergent subject matter and requires non-coextensive searches. It is noted to Applicant that the nucleic acid sequences encoding the KCNQ5 splice variants (SEQ ID NOs: 1-3) have been rejoined and are under consideration.

The requirement is still deemed proper and is therefore made FINAL.

Claims 41-48 are under consideration in the instant application.

### *Information Disclosure Statement*

1. The information disclosure statements (IDS) submitted on 01 February 2002 (Paper No. 8) and 22 August 2001 (Paper No. 7) have been considered in part by the examiner. The information disclosure statement filed on 22 August 2001 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It is noted to Applicant that the crossed off references are not present in the application.

### *Specification*

2. The disclosure is objected to because of the following informalities:

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (See page 21, line 1). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 41-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, wherein said polypeptide forms, with at least one additional KCNQ alpha subunit, a KCNQ potassium channel having the characteristic of voltage-gating; and wherein said nucleic acid specifically hybridizes under stringent conditions

to the nucleic acid of SEQ ID NOs: 1, 2, or 3 and that encodes an amino acid sequence of SEQ ID NO: 4 or 5, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamode, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS., does not reasonably provide enablement for an isolated nucleic acid encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, wherein said polypeptide forms, with at least one additional KCNQ alpha subunit, a KCNQ potassium channel having the characteristic of voltage-gating; and wherein said nucleic acid specifically hybridizes under stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 4 or 5, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamode, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims also recite an expression vector comprising the nucleic acid and a host cell transfected with the vector. The claims recite that the polypeptide encoded by the nucleic acid comprises an alpha subunit of a homomeric or heterimeric potassium channel.

The specification teaches that KCNQ5 polymorphic variants, orthologs, and alleles that are substantially identical to the conserved region of KCNQ5 can be isolated using KCNQ5 nucleic acid probes and oligonucleotides under stringent hybridization conditions, by screening libraries (pg 27, lines 20-23). However, the specification does not teach all possible nucleic acid variants that hybridize to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 4 or 5. The specification only discloses that the isolation and expression of the KCNQ5 gene (KCNQ5-1

and KCNQ5-2 splice variants; SEQ ID NOs: 2 and 3) in the *Xenopus* oocyte system produces a slow outward-rectifying potassium current that is activated by voltages as low as –80mV (pg 7, line 9-17; pg 60, lines 15-17; Figure 3).

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the nucleic acid and protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins (pg 26-41), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The art recognizes that function cannot be predicted from

structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Furthermore, one skilled in the art would not be able to predict that the claimed nucleic acid degenerates would encode a protein having biological activities similar to known KCNQ splice variants of SEQ ID NOs: 4 and 5. Relevant literature reports that potassium channels constitute the most diverse class of ion channels with respect to kinetic properties, regulation, pharmacology, and structure (pg 1329, col 2; Lehmann-Horn et al. Physiol Rev 79 (4): 1317-1372). The art acknowledges that function cannot be predicted based solely on structural similarity to a protein. For example, Lehmann-Horn et al. teach that a single point mutation in voltage-gated Kv1.1, the human homolog of the *Shaker* potassium channel, causes episodic ataxia with myokymia (pg 1351; Figure 15; Table 12).

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed polynucleotides to make biologically active KCNQ5 variants without resorting to undue experimentation to determine what the specific biological activities of the KCNQ5 variants are.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required

in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and that biological activity cannot be predicted based on structural similarity, and the breadth of the claims which fail to recite particular biological activities and also embrace a broad class of structural variants, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6. Claims 41-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the claims are directed to an isolated nucleic acid encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, wherein said polypeptide forms, with at least one additional KCNQ alpha subunit, a KCNQ potassium channel having the characteristic of voltage-gating; and wherein said nucleic acid specifically hybridizes under stringent conditions to a nucleic acid encoding an amino acid sequence of SEQ ID NO: 4 or 5, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamode, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS. The claims also recite an expression vector comprising the nucleic acid and a host cell transfected with the vector. The claims recite that the polypeptide encoded by the nucleic acid comprises an alpha subunit of a homomeric or heterimeric potassium channel.

The specification teaches that KCNQ5 polymorphic variants, orthologs, and alleles that are substantially identical to the conserved region of KCNQ5 can be isolated using KCNQ5 nucleic acid probes and oligonucleotides under stringent hybridization conditions, by screening libraries (pg 27, lines 20-23). However, the specification does not teach functional or structural characteristics of the polynucleotide variants in the context of a cell or organism. The description of the disclosed KCNQ5 nucleic acid genus (SEQ ID NO: 2, 3) is not adequate written description of the entire claimed genus of functionally equivalent polynucleotides.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to

lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only an isolated nucleic acid molecule encoding a polypeptide comprising an alpha subunit of a KCNQ potassium channel, wherein said polypeptide forms, with at least one additional KCNQ alpha subunit, a KCNQ potassium channel having the characteristic of voltage-gating; and wherein said nucleic acid specifically hybridizes under stringent conditions to the nucleic acid of SEQ ID NOs: 1, 2, or 3 and that encodes an amino acid sequence of SEQ ID NO: 4 or 5, wherein the hybridization reaction is incubated at 42°C in a solution comprising 50% formamode, 5x SSC, and 1% SDS and washed at 65°C in a solution comprising 0.2x SSC and 0.1% SDS , but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Conclusion***

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hu et al. WO 01/75108

Jegla, T. WO 01/70759

Jegla et al. Society for Neurosci Abs 26(1-2): Abs No. 714.1

Robbins et al. Pharmacol Ther 90(1) : 1-19, 2001.

Wicjenden et al. Br J Pharmacol 132(2) : 381-384, 2001.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
March 5, 2003